Synthesis of 3,3-Disubstituted 2,3-Dihydrobenzofuran Derivatives from Baylis-Hillman Adducts

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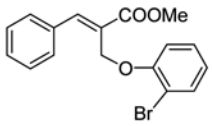
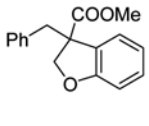
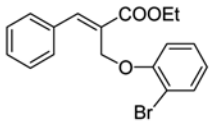
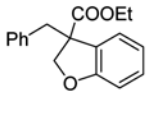
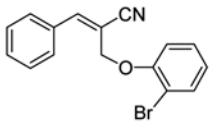
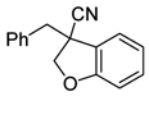
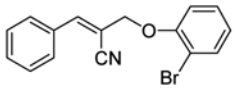
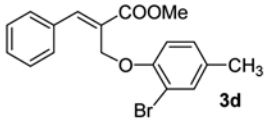
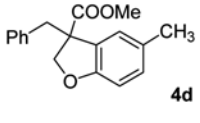
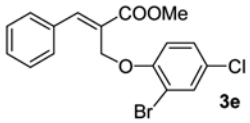
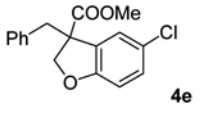
Dihydrobenzofuran derivatives are important synthetic intermediates and showed many biologically interesting activities.[1] However, synthetic methods for the compounds are rather limited.[2-4] Recently Trost and co-workers have reported the synthesis of dihydrobenzofuran derivatives starting from the Baylis-Hillman adducts by using the reductive Heck-type cyclization strategy.[3] Very recently, Lamaty and co-workers reported the synthesis of 3,3-disubstituted-2,3-dihydrobenzofuran derivatives *via* palladium-catalyzed cascade allylation-carbopalladation-Suzuki cross coupling strategy.[4]

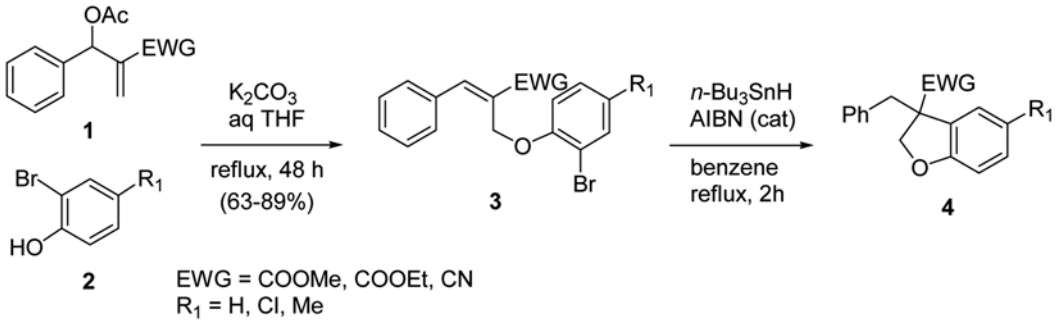
On the other hand, Shanmugam and Rajasingh have reported the synthesis of tetrahydrofuran backbone by the radical cyclization of triple bond containing cinnamate derivatives, which were synthesized from the Baylis-Hillman adducts.[5] They used vinyl radical, which was formed *via* the *in situ* hydrostannylation of triple bond.[5] We were stimulated by the results and envisioned that we could prepare 2,3-dihydrobenzofuran skeleton if we use aryl radical instead of the vinyl radical as shown in Scheme 1.[5]

Thus, we prepared the starting material **3a** from the reaction of the acetate of Baylis-Hillman adduct **1a** and 2-bromophenol (**2a**) as shown in Scheme 1. The starting material **3a** was converted to the desired 2-benzyl-2,3-dihydrobenzofuran-2-carboxylic acid methyl ester (**4a**),[4] the 5-*exo*-*trig* cyclization product, in 79% yield under the influence of *n*-Bu_3SnH/AIBN in benzene at refluxing temperature (entry 1 in Table 1). We could not isolate the corresponding dihydrobenzopyran derivative, the 6-*endo*-*trig* cyclization product, or simple reduction product. The optimum amounts of *n*-Bu_3SnH and AIBN were studied and

Table 1. Synthesis of 3,3-disubstituted 2,3-dihydrobenzofurans **4**[a]

Entry	Substrate **3**	Dihydrobenzofuran **4**	Yield (%)
1	 **3a**	 **4a**	79
2	 **3b**	 **4b**	68
3	 **3c-*Z***	 **4c**	67
4	 **3c-*E***	**4c**	72
5	 **3d**	 **4d**	65
6	 **3e**	 **4e**	62

[a]Conditions: *n*-Bu_3SnH (1.2 equiv), AIBN (20 mol%), benzene, reflux, 2 h.



Scheme 1

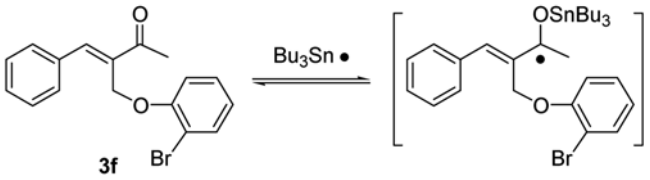


Figure 1

we found that slight excess of *n*-Bu_3SnH (1.2 equiv) and 20 mol% of AIBN gave the best results. By using this standard reaction conditions we prepared analogous dihydrobenzofuran derivatives **4b-e** in moderate yields and the results are summarized in Table 1. Stereochemistry of the starting materials did not alter the reaction pathway. As an example, we obtained the same compound **4c** either from the *E*-form and *Z*-form of **3c** (entries 3 and 4).

Radical cyclization of acetyl-substituted compound **3f** failed, unfortunately. In the reaction, starting material **3f** and small amounts of intractable mixtures were observed.[6] Instead of aryl radical generation by the abstraction of bromine atom, addition of *n*-Bu_3Sn radical to the carbonyl group of acetyl to generate the corresponding carbon-centered radical bearing tributylstannyloxy moiety might be favored (Figure 1).[7]

In summary, we disclosed the facile synthetic method of 3,3-disubstituted-2,3-dihydrobenzofurans starting from the acetates of Baylis-Hillman adducts by using radical cyclization strategy in moderate to good yields.

Experimental Section

Typical procedure for the synthesis of starting material 3a: To a stirred solution of the Baylis-Hillman acetate **1a** (234 mg, 1.0 mmol) and 2-bromophenol (206 mg, 1.2 mmol) in aq THF (5 mL, 1 : 1) was added K_2CO_3 (166 mg, 1.2 mmol) and the reaction mixture was heated to reflux for 48 h. After the usual workup and column chromatographic purification process (hexanes/ether, 20 : 1) we obtained **3a**, 284 mg (82%). Spectroscopic data of prepared starting materials **3a-f** are as follows.

Compound **3a**: 82%; colorless oil; IR (neat) 1716, 1477, 1234 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H), 4.90 (s, 2H), 6.86 (td, J = 7.7 and 1.5 Hz, 1H), 7.01 (dd, J = 8.4 and 1.5 Hz, 1H), 7.21-7.28 (m, 1H), 7.35-7.40 (m, 3H), 7.52-7.58 (m, 3H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.29, 64.24, 112.83, 114.70, 122.44, 126.90, 128.41, 128.67, 129.61, 129.78, 133.36, 134.33, 146.08, 155.10, 167.54.

Compound **3b**: 63%; colorless oil; IR (neat) 1712, 1477, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (t, J = 7.0 Hz, 3H), 4.30 (q, J = 7.0 Hz, 2H), 4.90 (s, 2H), 6.85 (td, J = 7.7 and 1.5 Hz, 1H), 7.02 (dd, J = 8.4 and 1.5 Hz, 1H), 7.21-7.29 (m, 1H), 7.35-7.41 (m, 3H), 7.53-7.58 (m, 3H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.22, 61.21, 64.31, 112.88, 114.83, 122.42, 127.26, 128.38, 128.64, 129.53, 129.77, 133.33, 134.41, 145.68, 155.19, 167.04.

Compound **3c**-*Z*: 35%; colorless oil; IR (neat) 2218, 1477, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.83 (s, 2H), 6.85-6.94 (m, 2H), 7.21-7.28 (m, 1H), 7.39-7.47 (m, 5H), 7.54-7.59 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 65.22, 110.59, 113.02, 114.52, 118.98, 123.33, 128.46, 129.00, 129.48, 130.45, 132.87, 133.76, 149.24, 154.16.

Compound **3c**-*E*: 54%; colorless oil; IR (neat) 2924, 2214, 1477 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.82 (d, J = 1.5 Hz, 2H), 6.89-6.98 (m, 2H), 7.25-7.32 (m, 1H), 7.41-7.46 (m, 4H), 7.58 (dd, J = 7.8 and 1.8 Hz, 1H), 7.78-7.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 69.83, 106.10, 112.92, 114.62, 117.12, 123.38, 128.62, 128.95, 129.17, 130.91, 132.81, 133.74, 145.49, 154.12.

Compound **3d**: 72%; colorless oil; IR (neat) 2951, 1716, 1493, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H), 3.85 (s, 3H), 4.86 (s, 2H), 6.92 (d, J = 8.4 Hz, 1H), 7.02-7.06 (m, 1H), 7.38-7.41 (m, 4H), 7.55-7.59 (m, 2H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.23, 52.32, 64.54, 112.62, 114.93, 127.09, 128.68, 128.87, 129.62, 129.86, 132.30, 133.74, 134.40, 146.02, 153.02, 167.66.

Compound **3e**: 67%; colorless oil; IR (neat) 1712, 1473, 1234 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (s, 3H), 4.87 (s, 2H), 6.94 (d, J = 9.0 Hz, 1H), 7.21 (dd, J = 8.7 and 2.4 Hz, 1H), 7.36-7.41 (m, 3H), 7.50-7.55 (m, 3H), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.36, 64.65, 113.33, 115.37, 126.58, 126.69, 128.25, 128.72, 129.73 (two peaks overlapped), 132.83, 134.23, 146.32, 153.98, 167.43.

Compound **3f**: 84%, colorless oil; IR (neat) 1670, 1477, 1242 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54 (s, 3H), 4.91 (s, 2H), 6.86 (td, J = 7.7 and 1.5 Hz, 1H), 7.04 (dd, J = 8.4 and 1.5 Hz, 1H), 7.22-7.61 (m, 7H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.22, 62.93, 112.62, 114.48, 122.39, 128.46, 128.76, 129.77, 129.84, 133.34, 134.38, 135.50, 145.57, 155.00, 198.45.

Typical procedure for the radical cyclization of 3a to 4a: To a stirred mixture of **3a** (104 mg, 0.3 mmol) and *n*-Bu_3SnH (105 mg, 0.36 mmol) in benzene (5 mL) was added AIBN (10 mg, 0.06 mmol) and the reaction mixture was heated to reflux for 2 h. After the usual workup and column chromatographic purification process (hexanes/ether, 20 : 1) we obtained **4a**, 63 mg (79%). Spectroscopic data of prepared compounds **4a-e** are as follows.

Compound **4a**: 79%; colorless oil; IR (film) 2954, 1736, 1597, 1481 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10 (d, J = 13.8 Hz, 1H), 3.47 (d, J = 13.8 Hz, 1H), 3.74 (s, 3H), 4.51 (d, J = 9.9 Hz, 1H), 4.88 (d, J = 9.9 Hz, 1H), 6.76-6.79 (m, 1H), 6.91 (td, J = 7.8 and 1.2 Hz, 1H), 6.99-7.06 (m, 2H), 7.16-7.28 (m, 4H), 7.36-7.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 44.24, 52.71, 57.88, 76.79, 110.26, 120.87, 125.30, 127.29, 128.60, 128.62, 129.77, 129.79, 136.38, 159.72, 173.06.

Compound **4b**: 68%; colorless oil; IR (film) 2981, 1732, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 3.10 (d, J = 13.8 Hz, 1H), 3.47 (d, J = 13.8 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.51 (d, J = 9.6 Hz, 1H), 4.90 (d, J = 9.6 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.91 (td, J = 7.5 and 1.2 Hz, 1H), 7.01-7.05 (m, 2H), 7.16-7.27 (m, 4H), 7.39 (dd, J = 7.5 and 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.06, 44.07, 57.54, 61.50, 76.56, 110.00, 120.60, 125.06, 127.03, 128.34, 128.53, 129.49, 129.60, 136.24, 159.50, 172.32.

Compound **4c**: 67% and 72% (see Table); colorless oil; IR

(film) 2924, 2241, 1597, 1481 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10 (d, J = 7.5 Hz, 1H), 3.20 (d, J = 7.5 Hz, 1H), 4.62 (s, 2H), 6.84-6.88 (m, 1H), 6.93 (td, J = 7.5 and 1.2 Hz, 1H), 7.05-7.09 (m, 1H), 7.18-7.34 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 44.06, 46.39, 78.05, 110.73, 120.56, 121.51, 124.50, 126.31, 127.89, 128.60, 130.19, 130.63, 133.95, 158.97.

Compound **4d**: 65%; colorless oil; IR (film) 2951, 1736, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.05 (d, J = 13.8 Hz, 1H), 3.49 (d, J = 13.8 Hz, 1H), 3.74 (s, 3H), 4.48 (d, J = 9.6 Hz, 1H), 4.86 (d, J = 9.6 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.98-7.05 (m, 3H), 7.19 (s, 1H), 7.23-7.26 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 20.86, 43.96, 52.49, 57.71, 76.60, 109.57, 125.31, 127.04, 128.39, 128.43, 129.52, 130.02, 130.04, 136.30, 157.36, 172.88.

Compound **4e**: 62%; white solid, mp 73-74 °C; IR (neat) 2954, 1736, 1477 cm^{-1}; ^1H NMR ($CDCl_3$) δ3.09 (d, J = 13.8 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.76 (s, 3H), 4.52 (d, J = 9.6 Hz, 1H), 4.88 (d, J = 9.6 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.97-7.02 (m, 2H), 7.14 (dd, J = 8.7 and 2.4 Hz, 1H), 7.22-7.29 (m, 3H), 7.33 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 44.04, 52.67, 57.71, 77.07, 111.00, 125.27, 125.34, 127.26, 128.47, 129.48, 129.50, 130.06, 135.60, 158.17, 172.22.

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